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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/832,015 | 04/10/2001 | Nancy J. Woolf | NJW-1 | 9668 |

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| EXAMINER |
|---|
| NICHOLS, CHRISTOPHER J |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | |

DATE MAILED: 08/25/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/832,015 | WOOLF ET AL. | |
| | Examiner | Art Unit | |
| | Christopher Nichols, Ph.D. | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *10-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 July 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Status of Application, Amendments, and/or Claims*

1. The Amendment filed 28 July 2003 (Paper No. 6) has been received and entered *in part*. Claims 1, 3, 4, 5, 6, 7, and 8 have been amended.

2. Applicant's election of Group I (claims 1-9) in Paper No. 3 (9 October 2002) was acknowledged in the previous Office Action (Paper No. 5, 24 January 2003). Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement in the response filed 9 October 2002, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 10-19 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

### *Withdrawn Objections And/Or Rejections*

3. The objections to the Specification as set forth at pp. 3 ¶5-8 in the previous Office Action (Paper No. 5, 24 January 2003) is *withdrawn* in view of Applicant's amendments (Paper No. 6, 28 July 2003).

4. The objection to claim 1 as set forth at pp. 4 ¶9 in the previous Office Action (Paper No. 5, 24 January 2003) is *withdrawn* in view of Applicant's amendments (Paper No. 6, 28 July 2003).

5. The rejections of claims 3, 4, 5, 6, 7, and 8 under 35 U.S.C. §112 ¶2 as set forth at pp. 4-5 ¶10-11 in the previous Office Action (Paper No. 5, 24 January 2003) is *withdrawn* in view of Applicant's amendments (Paper No. 6, 28 July 2003).

***Maintained Objections And/Or Rejections***

***New Objections And/Or Rejections***

6. The amendment filed 28 July 2003 (Paper No. 6) is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The deletion of "haloperidol" constitutes new matter as alters the subject matter of the Specification as filed. Applicant is required to cancel the new matter in the reply to this Office Action.

7. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference sign(s) not mentioned in the description: the numbers present in Figures 1 and 2. A proposed drawing correction, corrected drawings, or amendment to the specification to add the reference sign(s) in the description, are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

8. Claim **9** is objected to because of the following informalities: two periods between "(Original)" and "The". Appropriate correction is required.

***New Rejections***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims **1-9** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

10. The claims are drawn very broadly to a method of treating Alzheimer's disease via administration of an antagonist of a neurotransmitter receptor which indirectly inhibits phosphorylation of microtubule-associated protein-2 and then administering to said patient an anticholinesterase agent in humans. The language of said claims encompasses a massive genus of as of yet unspecific neurotransmitter antagonists, none of which are identified by the Specification as filed.

11. The specification teaches a prophetic process by which one can identify a neurotransmitter antagonist with the properties necessary to satisfy the limitations of claim 1. In addition, the Specification prophetically considers practicing the claimed method with the unidentified neurotransmitter receptor antagonist and an anticholinesterase agent utilizing a "sensor" to monitor the progress of the therapy.

12. The specification fails to provide any guidance for the successful use or assessment of the claimed method, and since resolution of the various complications in regards to treating Alzheimer's disease is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to

practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations of antagonists of neurotransmitter receptors, characterize them, and then test them for suitability to practice the claimed invention. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed method treating Alzheimer's disease in a patient.

13. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a prophetically considered compound *in vivo* based solely on its predicated performance as highly problematic (see MPEP 2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods in *in vivo* therapeutic assays, such a disclosure would not be considered enabling since the state of Alzheimer's disease is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

14. Concerning the breadth of the claims and the nature of the invention as a therapeutic, as noted above, no examples of compounds, antibodies, nucleic acids, proteins, or other "antagonists" are provided by the instant Specification as filed or the prior art that meet the limitations of claim 1 and would be useful for treating Alzheimer's disease. While putting forth the proposition of using a neurotransmitter receptor antagonist for treating Alzheimer's disease, no evidence is present in the instant Specification or the prior art as to guide the skilled artisan to identify or use the desired neurotransmitter receptor antagonist as a therapeutic. What remains is an invitation to experiment, first to determine which neurotransmitter antagonist satisfies the limitations of claim 1, and then determine its role, and finally the course of therapy that would have a salubrious outcome {see MPEP §2164.01(a)}. Thus in the absence of guidance and working examples, the skilled artisan is confronted with an undue burden of experimentation in an unpredictable and undeveloped art to practice the invention as claimed.

15. On the amount of guidance provided by the Specification, no compounds have been disclosed that have the activity required by the claims. Screening for such compounds is an act of invention, for which insufficient guidance is provided in this Specification. Thus the Specification fails to teach the skilled artisan how to make the antagonists recited in the claims.

16. The following references are cited herein to illustrate the state of the art of Alzheimer's disease.

17. Concerning the nature of the invention, as the Specification suggests using antagonists of muscarinic acetylcholine receptors, Fisher (2000) "Therapeutic Strategies in Alzheimer's Disease" M1 Muscarinic Agonists." Jpn. J. Pharmacol. **84**: 101-112 and Forlenza *et al.* "Muscarinic agonists reduce tau phosphorylation in non-neuronal cells via GSK-3b inhibition

and in neurons." J. Neural. Transm. **107**: 1201-1212 both teach that muscarinic agonists alter the metabolism of amyloid precursor protein leading to an increase in a-secretase cleavage and a decreased production of amyloidogenic peptides. This suggests that said compounds may have a therapeutic effect. Thus the nature of the invention runs contrary this evidence as both are silent on antagonists as therapeutics as well as the role of MAP-2 in Alzheimer's disease therapy.

18. On the prior art, as the Specification suggests that M1 antagonists may be used in the screening steps of the invention, Fisher *et al.* (17 January 1996) "M1 Agonists for the treatment of Alzheimer's disease. Novel properties and clinical update." Ann. N Y Acad. Sci. **777**: 189-196 teaches that M1 agonists may be useful as therapeutics for Alzheimer's especially due to the relationship between decreased phosphorylation of tau protein via m1AchR (pp. 194). The reference is silent, however, on the subject of indirect phosphorylation, antagonists, and the role of MAP-2 phosphorylation thus offering no support to the claimed method.

19. Finally the specification does not provide a nexus between the method and a therapeutic outcome in Alzheimer's patients. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying prophetic guidance to the *in vivo* treatment of Alzheimer's disease as exemplified in the references herein.

20. Claims **1-9** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

21. The claims are drawn to a method of administering a neurotransmitter receptor antagonist which indirectly inhibits phosphorylation of microtubule-associated protein-2 (MAP-2), causes the phosphorylation of MAP-2 in limbic cells, and causes the phosphorylation of MAP-2 in neocortical cells. The claims require specific biological activities which are contradictory. It is not clear how an antagonist can indirectly inhibit phosphorylation of MAP-2 while simultaneously leading to the phosphorylation of the same protein two different cell populations. Thus, the claims are drawn to an ill-defined genus of antagonists which are defined by simultaneous and contradictory biological activities.

22. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is the aforementioned contradictory activities. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. No active variants are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus.

23. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

24. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

25. Therefore the full breadth of the claims do not meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

26. Claims **1** and **4** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

27. The term "indirectly inhibits" in claim 1 is a relative phrase which renders the claim indefinite. The term " indirectly inhibits " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would

not be reasonably apprised of the scope of the invention. The metes and bounds of what is meant by "indirectly inhibits" is not clear from the Specification or the prior art.

28. The term "most current" in claim 4 is a relative term which renders the claim indefinite. The term " most current" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of what is meant by "most current" is not clear from the Specification or the prior art.

***Summary***

29. Claims 1-9 are hereby rejected.

30. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

a. US 5668117 (16 September 1997) Shapiro

b. US 5683422 (4 November 1997) Rise

c. Lahiri *et al.* (2002) "Regulation of APP Processing with Cholinesterase Inhibitors." Research and Practice in Alzheimer's Disease **6**: 338-344

d. Hellström-Lindahl (30 March 2000) "Modulation of β-amyloid precursor protein processing and tau phosphorylation by acetylcholine receptors." European Journal of Pharmacology **393**(1-3): 255-263.

e. Pavía *et al.* (1998) "Alzheimer's disease: relationship between muscarinic cholinergic receptors b-amyloid and tau proteins." Fundam. Clin. Pharmacol. **12**(5): 473-481.

f. Fisher *et al.* (August-October 2002) "AF150(S) and AF267B: M1 Muscarinic Agonists as Innovative Therapies for Alzheimer's Disease." Journal of Molecular Neuroscience **19**(1-2): 145-153

## *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
August 19, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER